# A multicenter, randomized, open-label, blinded-assessor, phase 4 study in patients with early rheumatoid arthritis to compare active conventional therapy versus three biologic treatments, and two de-escalation strategies in patients who respond to treatment.

Published: 22-02-2017
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| | |
|---|---|
| **Ethical review** | Approved WMO |
| **Status** | Recruitment stopped |
| **Health condition type** | Autoimmune disorders |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON50439

**Source**
ToetsingOnline

**Brief title**
NORD-STAR

### Condition

- Autoimmune disorders

**Synonym**
arthritis, Rheumatoid Arthritis

**Research involving**
Human

## Sponsors and support

**Primary sponsor:** Ronald van Vollenhove/Karolinska Instituut (clinTRID)
**Source(s) of monetary or material Support:** Bristol-Myers Squibb,Reade,UCB Pharma

## Intervention

**Keyword:** biologicals, conventional therapy, de-escalation, early rheumatoid arthritis

## Outcome measures

### Primary outcome

Primary study outcome for both the first part as the second part of de study is

the proportion of patients in remission at week 24 after start resp. after dose

reduction, as defined by CDAI.

### Secondary outcome

Secondary outcomes are remission on all timepoints, DAS28, morning stiffness,

several questionaires (a.o. HAQ, VAS) e.t.c. Also the Sharp van der Heijden

score after 48 week will be investigated.

# Study description

### Background summary

The most important factor for a good prognosis for patients with rheumatoid arthritis is treatment in the early stages of the disease. By treating early, a good and fast response to treatment and a more permanent improvement of the disease can be expected in the long term. The standard treatment of rheumatoid arthritis consists of Methotrexate in combination with non-biological drugs as a first choice - or a combination with biological drugs as an alternative. Recently, there have been recommendations and guidelines advocating initiation of biologics for patients with high disease activity and poor prognosis.

### Study objective

The objective of the study is to compare conventional therapy with biological therapy in patients with early rheumatoid arthritis.

### Study design

Randomized open-label phase 4 study

### Intervention

Part 1. (week 0-80)
Randomization to:
a) Conventional therapy (methotrexate + prednisolone)
b) Certolizumab (+ methotrexate)
c) Abatacept (+ methotrexate)
d) Tocilizumab (+ methotrexate) --> This treatment arm was removed after safety warning from Roche in combination with the EMA reporting acute liver failure with liver transplantation in rare cases. (dear doctor letter 27-06-2019)

Part 2. (starts when patients achieves remission between week 48-80)
Randomization to:
a) direct de-escalation of the medication
b) de-escalation of the medication with a delay of 24 weeks

### Study burden and risks

Patients will have to visit the center more frequently than during regular care, also more intensive assessments will be performed. This also means that the health status of the patients will be monitored more intensively and this may in turn lead to better treatment outcomes. The risks associated with participation are mostly caused by medication (allergic reactions, slightly higher susceptibility to infections), these risks are comparable to risks associated with general care for rheumatoid arthritis.

## Contacts

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# Trial sites

## Listed location countries

Netherlands

# Eligibility criteria

**Age**
Adults (18-64 years)
Elderly (65 years and older)

## Inclusion criteria

1. Subject is >=18 years of age., 2. Subject has a diagnosis of RA as defined by the newly established ACR/EULAR criteria, 2010 (Appendix D). (Patients should also be classified according to the 1987-revised ACR-classification criteria, without this being an inclusion criteria) (Appendix C)., 3. <24 months from arthritis symptom debut (symptom duration will be registered)., 4. Subject must have DAS28 (CRP) > 3.2., 5. >= 2 swollen joints AND >= 2 tender joints., 6. Subject must fulfill one of the following three criteria: RF positive OR ACPA positive OR CRP >=10 mg/L., 7. Female subject is either not of childbearing potential (postmenopausal, surgically sterile etc.), or is of childbearing potential and practicing one of the following methods of birth control throughout the study and for 150 days after study completion:
• Intrauterine device (IUD)
• Contraceptives (oral, parenteral, patch) for three months prior to study drug administration)
• A vasectomized partner
8. Female subjects of childbearing potential must have a negative serum pregnancy test at the Screening visit., 9. Subject is judged to be in good general health as determined by the principal investigator based upon the results of medical history, laboratory profile, physical examination, chest X-ray (CXR), and 12-lead electrocardiogram (ECG) performed at Screening., 10. Subjects must be able and willing to provide written informed consent and comply with the requirements of this study protocol., 11. Subjects must be able and willing to self-administer s.c. injections or have a qualified person

available to administer s.c. injections.

## Exclusion criteria

1. Subject has been previously treated with disease modifying antirheumatic drugs (DMARDs) for rheumatic diseases., 2. Current active inflammatory joint disease other than RA., 3. Subjects has had a dose of prednisone (or equivalent) >7.5 mg/day or has had a dose change within the preceding 4 weeks., 4. Subject has been treated with intra-articular or parenteral administration of corticosteroids in the preceding 4 weeks. Inhaled corticosteroids for stable medical conditions are allowed., 5. Subject has undergone joint surgery within the preceding two months (at joints to be assessed within the study)., 6. Subject has chronic arthritis diagnosed before age 17 years., 7. Subject has a history of an allergic reaction or significant sensitivity to constituents of study drugs., 8. Subject has been treated with any investigational drug within one month prior to screening visit., 9. Active infection of any kind (excluding fungal infections of nail beds), or any major episode of infection requiring hospitalization within 4 weeks of screening., 10. Subject has a poorly controlled medical condition, such as uncontrolled diabetes, unstable heart disease, congestive heart failure, recent cerebrovascular accidents and any other condition which, in the opinion of the investigator, would put the subject at risk by participation in the study., 11. Subject has a history of clinically significant hematologic (e.g., severe anemia, leukopenia, thrombocytopenia), renal or liver disease (e.g., fibrosis, cirrhosis, hepatitis)., 12. Subject has history of neurologic symptoms suggestive of central nervous system (CNS) demyelinating disease and/or diagnosis of central demyelinating disease., 13. Subject has history of cancer or lymphoproliferative disease. Allowable exceptions:
a. Successfully treated cutaneous squamous cell or basal cell carcinoma
b. Localized carcinoma in situ of the cervix
c. Curatively treated malignancy (treatment terminated) > 5 years prior to screening, 14. Subject has a history of listeriosis, histoplasmosis, untreated TB, persistent chronic infections, or recent active infections requiring hospitalization or treatment with intravenous (iv) anti-infectives within 30 days or oral anti-infectives within 14 days prior to the BL visit., 15. Subjects will be evaluated for latent TB infection with a PPD or QuantiFERON test and X-ray. Subjects with evidence for latent TB will not be enrolled but first assessed according to local guidelines., 16. Subject is known to have immune deficiency, history of Human Immunodeficiency Virus (HIV) or is otherwise severely immunocompromised., 17. Female subject who is pregnant or breast-feeding or considering becoming pregnant during the study or within 150 days after the last dose of study medication., 18. Subject has a history of clinically significant drug or alcohol usage in the last year., 19. Subject has a chronic widespread pain syndrome., 20. Subject is considered by the investigator, for any reason, to be an unsuitable candidate for the study., 21.

Subject is unwilling to comply with the study protocol., 22. Screening clinical laboratory analyses show any of the following abnormal laboratory results:
a. Aspartate transaminase (AST) or alanine transaminase (ALT) > 1.75 times upper limit of normal (ULN).
b. Positive serum human chorionic gonadotropin (hCG).
c. Positive tests for hepatitis B surface antigen (HBsAg) or hepatitis C serology indicative of current infection.
d. Creatinine levels > 2x the ULN. If creatinine 1-2 times ULN, check GFR.
e. Hemoglobin < 90 g/L.
f. Absolute neutrophil count (ANC) < 1.5 x 10^3/microL.
g. Serum total bilirubin >= 1.5 mg/dL (>= 26 micromol/L).

# Study design

## Design

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|---|---|
| Study phase: | 4 |
| Study type: | Interventional |
| Intervention model: | Parallel |
| Allocation: | Randomized controlled trial |
| Masking: | Open (masking not used) |
| Control: | Active |
| Primary purpose: | Treatment |

## Recruitment

NL

| | |
|---|---|
| Recruitment status: | Recruitment stopped |
| Start date (anticipated): | 25-09-2017 |
| Enrollment: | 120 |
| Type: | Actual |

## Medical products/devices used

| | |
|---|---|
| Product type: | Medicine |
| Brand name: | - |
| Generic name: | Metothrexate |
| Registration: | Yes - NL intended use |

| | |
|---|---|
| Product type: | Medicine |
| Brand name: | - |
| Generic name: | Prednisolon |
| Registration: | Yes - NL intended use |
| Product type: | Medicine |
| Brand name: | Cimzia |
| Generic name: | Certolizumab pegol |
| Registration: | Yes - NL intended use |
| Product type: | Medicine |
| Brand name: | Orencia |
| Generic name: | Abatacept |
| Registration: | Yes - NL intended use |

## Ethics review

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|---|---|
| Approved WMO Date: | 22-02-2017 |
| Application type: | First submission |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 22-03-2017 |
| Application type: | First submission |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 16-02-2018 |
| Application type: | Amendment |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 29-08-2019 |
| Application type: | Amendment |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 24-12-2020 |
| Application type: | Amendment |
| Review commission: | METC Amsterdam UMC |

# Study registrations

## Followed up by the following (possibly more current) registration

No registrations found.

## Other (possibly less up-to-date) registrations in this register

No registrations found.

## In other registers

| Register | ID |
|---|---|
| EudraCT | EUCTR2011-004720-35-NL |
| ClinicalTrials.gov | NCT01491815 |
| CCMO | NL60775.048.17 |